

requests deletion of the present Sequence listing and substitution of the newly submitted listing. No new matter has been added.

The abbreviation for the term "TPA" has been written out in the first instance on page 2, line 22.

Applicant respectfully requests reconsideration of the present application.

THE INVENTION

The present invention provides a novel member of the mitogen activated protein kinase family (MAPK) referred to as c-Jun N-terminal kinase (JNK) and polynucleotides encoding JNK. The JNK of the invention includes two isoforms expressed by most cells. These two proteins are 46 kD and 55 kD in size and are termed JNK1 and JNK2. Recently, a cDNA clone encoding the 46 kD isoform, JNK1, was isolated. Sequence analysis of JNK1 identified it as a novel and distant member of the MAP kinase group of signal transduction enzymes.

The MAPK cascade is a major signaling system by which cells transduce extracellular cues into intracellular responses. The mammalian MAPK subtypes can be activated simultaneously via distinct parallel cascades in response to the same stimuli. The MAPKs include the ERKs, ERK1 and ERK2, the JNK/SAPK subfamily (JNK1, JNK2, SAPK α (MAP-2 or pp54), SAPK β , SAPK γ) and the HOG1 homologue, p38).

The invention provides a screen for compositions which affect JNK kinase (*e.g.*, inhibit or stimulate kinase activity or expression).

I. REJECTIONS UNDER 35 USC§112

Claims 12, 13, and 16 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses this rejection.

Claims 13 and 16 have been canceled and therefore the rejection is moot with respect to these claims. Claim 12 has been amended to recite c-Jun rather than c-jun, thereby overcoming the rejection. Applicant requests that this rejection be withdrawn.

II. REJECTIONS UNDER 35 U.S.C. §103

Claims 12 and 14-17 stand rejected under 35 U.S.C. §103 as being unpatentable over Adler, *et al.*, and Pulverer, *et al.* Applicant respectfully traverses this rejection.

The two cited references teach a c-Jun N-terminal kinase. Pulverer and Adler teach pp42 (ERK2) and pp44 (ERK1) MAP kinases that phosphorylate Serine 63 and 73 of c-jun.

Applicant has amended claim 12 to recite the c-Jun N-terminal kinase (JNK) of the invention.

In order to establish a prima facie case of obviousness, the combination of cited references must teach or suggest the claimed invention. In addition, there must be some teaching, suggestion or incentive supporting the combination of cited references. (ACS Hospital Systems, Inc. v. Montefiore Hospital, 732 F. 2d 1572, 1577, 221 USPQ 329, (Fed. Cir. 1984)). References cannot be arbitrarily combined and there must be some reason why one skilled in the art would be motivated to make the proposed combination of primary and secondary references. (In re Nomiya, 184 USPQ 607 (CCPA 1975)). The test for combining references is what the combination of disclosures taken as a whole would suggest to one of ordinary skill in the art. (In re McLaughlin, 170 USPQ 209 (CCPA 1971)).

Applicant submits that the enzymes taught in the cited references are distinct from JNK of the present claims, and therefore, the DNA encoding JNK proteins of the invention must be distinct. JNK is related to ERK2(pp42) and ERK1 (pp44) ERK/MAP kinases, however, they are distinct kinases encoded by distinct DNA sequences. Applicants have provided a publication by Hibi, *et al.* (Appendix A) which supports the novelty of the kinase of the present invention.

The MAP/ERK proteins are characterized by their ability to phosphorylate myelin basic protein (MBP), as opposed to the substrate specificity of JNKs, which do not phosphorylate MBP. As shown in FIGURE 6a of Hibi, *et al.*, purified ERK1/2 (a mixture of both enzymes) phosphorylated MBP 55-fold more efficiently than GSTc-Jun(wt), whereas JNK phosphorylated GSTc-Jun(wt) 25-fold more efficiently than MBP. In addition, JNK phosphorylated GSTc-Jun(wt) 30-fold more efficiently than GSTvJun (1-144), whereas ERK1/2 did not display significant preference for either substrate.

On page 2139, column 1, first full paragraph, Hibi, *et al.*, state:

"Further indications that JNK differs from previously characterized MAP/ERKs are provided by Western blotting experiments showing that JNK does not cross-react with an anti-ERK antiserum...capable of detecting both ERK1 and ERK2 (Fig. 6B). In addition, probing of Western blots with two different anti-phosphotyrosine antisera...failed to detect the presence of this phosphorylated residue in JNK, whereas ERK1 was clearly reactive (Fig. 6...these results suggest that JNK is a novel proline-directed extracellular signal-responsive kinase."

Applicants provide further support for the functional distinctiveness of JNK compared to ERK1 (Adler) and ERK2 (Pulverer) in Appendix B, Minden, *et al.*, attached herein. Minden shows that unlike JNKs, ERK1 and ERK2 do not phosphorylate the N-terminal sites of c-Jun in vitro; instead they phosphorylate an inhibitory C-terminal site. Furthermore, the phosphorylation of c-Jun in vivo at the N-terminal sites correlates with activation of the JNKs, but not the ERKs (see page 6684, second column, through page 6687). In addition, while both ERK1 and ERK2 and JNK are activated by growth factors, JNK is preferentially activated in response to UV irradiation and TNF- α , which have little effect on ERK activity (FIGURE 3, page 6686).

Applicants also provide Appendix C which is a review article which acknowledges that there are distinct MAPKs, which include ERKs and a separate class known as JNKs (see illustration in FIGURES 1 and 3 for example). The JNKs described in the review are the proteins of the present invention.

Finally, Appendix D, Derijard, *et al.* shows the cDNA sequence encoding JNK, which is distinct from other MAPKs, including ERK1 and ERK2 of Adler and Pulverer (see FIGURE 1A-C).

Consequently, in light of the amendment to claim 12 and the supportive evidence in Appendices A-D, Applicant submits that it would not have been obvious to use Applicant's novel JNK kinase or polynucleotide encoding the kinase in an assay to determine the effect of a composition on that novel kinase.

Therefore, Applicant requests that this rejection be withdrawn.

In summary, for the reasons set forth herein, Applicants maintain that claims 12, 14, 15 and 17 clearly and patentably define the invention, respectfully request that the Examiner reconsider the various grounds set forth in the Office Action, and respectfully request the allowance of the claims which are now pending.

If the Examiner would like to discuss any of the issues raised in the Office Action, Applicant's representative can be reached at (619) 678-5070.

Please charge any additional fees, or make any credits, to Deposit Account No. 06-1050.

Respectfully submitted,

Date: 1/22/96

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